CASE REPORT

Primary CNS lymphoma in a patient treated with azathioprine

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SUMMARY

A 33-year-old man treated with azathioprine for 12 years for Crohn's disease presented with headache, nausea and vomiting accompanied by difficulty in putting words together and slight mental confusion. Prednisolone and antibiotics were without effect. MRI of the brain showed multiple focal lesions with surrounding oedema. There was cerebrospinal fluid pleocytosis, and Epstein-Barr virus (EBV) DNA was detected in the spinal fluid by PCR. A brain biopsy confirmed the suspicion of primary brain lymphoma. EBV-associated primary brain lymphoma is a relevant differential diagnosis in patients with long-standing immune suppression presenting with neurological symptoms. Detection of EBV DNA in the spinal fluid together with characteristic radiological findings may serve as a diagnostic clue for a quick diagnosis.

BACKGROUND

Patients treated with thiopurines may develop severe CD4 cell lymphocytopenia. If the patient has a latent Epstein-Barr virus (EBV) infection there is a risk of developing EBV-driven lymphomas. Primary central nervous system lymphoma (PCNSL) is quite rare but must be kept in mind in patients with immunosuppression presenting with neurological symptoms.

CASE PRESENTATION

We present the case of a 33-year-old man with Crohn's disease (CD) who was admitted to hospital in September 2013 with rectal bleeding and haematemesis. He was diagnosed with CD in 1999 and was treated with azathioprine 150 mg once daily as maintenance therapy for at least 12 years. In the summer of 2013, he developed a flare in his colitis and was started on prednisone 40 mg/day. At the time of admission, he was tapering down prednisone and had a 1-week history of migraine-like symptoms with headache, nausea and vomiting.

Increasing activity in CD was suspected and the prednisone dose was increased. A gastroscopy revealed Mallory-Weiss lesions but was otherwise normal. The clinical condition stabilised and the patient was discharged with prednisone 50 mg/day. Azathioprine was continued.

Four days later he was readmitted with abdominal pain, headache and vomiting. He was slightly confused and had difficulty putting words together. Apart from this he was neurologically intact. A brain CT scan revealed three focal lesions in the left temporal lobe with surrounding oedema. MRI was

performed raising the suspicion of multiple brain abscesses (figure 1), possibly septic emboli, and treatment was initiated with meropenem 6 g/day and gentamicin 240 mg/day supposing endocarditis to be the source of the emboli. Transoesophageal echocardiography was, however, with no signs of endocarditis and no bacteria were cultured from his blood.

Antibodies against HIV, *Toxoplasma gondii* or cytomegalovirus were not detected in the blood. Tests for *Aspergillus* galactomanan antigen and PCR for *Mycobacterium tuberculosis* and polyomavirus all came out negative. Blood investigations showed leucocytosis of $13.5 \times 10^9/L$ ($3.5\text{--}8.8 \times 10^9/L$) but with lymphocytopenia $0.1 \times 10^9/L$ ($1.00\text{--}4.00 \times 10^9/L$) with $50 \times 10^6/L$ CD4 T cells ($300\text{--}1700 \times 10^6/L$) and $20 \times 10^6/L$ CD8 T cells ($220\text{--}880 \times 10^6/L$).

A lumbar puncture was performed showing pleocytosis with $18 \times 10^6/L$ mononuclear leucocytes ($<5 \times 10^6/L$), $14 \times 10^6/L$ polymorphonuclear leucocytes ($<1 \times 10^6/L$) and $78 \times 10^6/L$ erythrocytes (0). The cerebrospinal fluid (CSF) protein level was 0.96 g/L (0.15–0.50 g/L) and the glucose level was 3 mmol/L. Flowcytometry revealed 21.6% immunophenotypically normal lymphocytes and no malignant cells. Microscopic examination of the CSF showed no signs of bacteria or fungus. An elevated EBV DNA count of $>54\,000$ copies/mL was detected by PCR. EBV DNA was also found in peripheral blood although in lesser quantities of 1460 copies/mL. The patient started treatment with valaciclovir 1 g three times daily to suppress EBV replication, and a new CSF PCR 5 days later showed a rapid decline in EBV DNA to 9239 copies/mL.

Following the finding of EBV in the CSF, intracerebral lymphoma was suspected and a brain biopsy was performed. The biopsy revealed large, proliferating, Epstein-Barr early region (EBER)-positive B cells containing up to several nucleoli and a diagnosis of diffuse large B-cell lymphoma with EBER positivity resulting from immunosuppression was established (figure 2). A bone marrow biopsy and a PET CT scan showed no signs of disseminated disease, and the patient was diagnosed with PCNSL.

TREATMENT

The optimal treatment of PCNSL is unknown but high-dose systemic methotrexate is considered standard treatment, often in combination with other CNS penetrating cytotoxic agents such as high-dose cytarabine. At our institution we treat PCNSL according to a modified 'Bonn regimen',¹

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Figure 1 (A) MRI fluid attenuated inversion recovery with bilateral white matter hyperintensities. (B) MRI T1 C+ with patchy enhancement of the lesions.

containing sequential therapy with high-dose methotrexate (hd MTX), cytarabine, cyclofosfamide, ifosfamide, vincristine, vinblastine and dexamethasone combined with intrathecal (IT) cytarabine alone without IT prednisone and IT MTX, delivered by lumbar puncture, hence not by an Ommaya reservoir as in the original protocol. In the present case, rituximab was administered with every course. Owing to severe neurotoxicity after three courses of chemotherapy, the treatment schedule was modified and the patient received another three courses of hd MTX and procarbazine plus prednisolone. The patient obtained a complete remission (CR) and remains in CR with short follow-up of 4 months.

DISCUSSION

EBV is a member of the gammaherpesvirinae subfamily of viruses. It causes infectious mononucleosis but is also associated

with malignant disease such as Burkitt lymphoma, Hodgkin's disease and immunodeficiency-associated B-cell lymphomas in immunocompromised patients.

There is general consensus that inflammatory bowel disease (IBD) itself does not increase the risk of cancer, and that the severity of the disease does not influence on this risk.^{2 3} However, several studies have found that treatment with thiopurines in patients with IBD increases the risk of developing lymphoma by 4–6 times. The increased risk is related to the duration of the treatment^{4 5} and returns to the level of the background population once treatment is stopped.² Most of these lymphomas are of the diffuse large B-cell type and are EBV positive.^{3 4}

PCNSL is a rare condition accounting for around 2% of all cerebral malignancies in immunocompetent patients.⁶ Most cases are aggressive diffuse large B-cell lymphomas with a poor

Figure 2 Giemsa stain of the cerebral biopsy showed large lymphoid cells with irregular nuclei and one to three nucleoli (A). Immunohistochemical staining showed strong expression of CD20 (B). Other positive markers were PEX5, Bcl2, CD30 and IRF4/MUM1, while CD10 was focally positive. T-cell markers and cyclin D1 were negative (not shown). Ki67 staining revealed a high proliferation rate (C). *In situ* hybridisation showed strong Epstein-Barr early region positivity (D).

prognosis. The diagnostic method of choice is a cranial MRI with contrast followed by biopsy. In immunocompromised patients the MRI is characterised by multiple lesions with a ring-like enhancement with a well-defined surrounding oedema.⁷ The radiological and also the histopathological findings may be clouded by the administration of steroids. In this case, a definitive histopathological diagnosis was obtained; despite that, therapy with high-dose prednisolone was initiated before the biopsy. It is, however, important to underline that a biopsy should be obtained before the administration of prednisolone whenever possible since it is well documented that glucocorticoids may impair the pathological and radiological diagnosis of PCNSL.

Patients treated with immunomodulatory drugs often have an iatrogenically induced dysfunction or quantitative reduction of their CD4 and CD8 lymphocytes and, therefore, the development of lymphoma in this patient group is quite similar to that seen in patients with post-transplant-like disease (PTLD) or patients infected with HIV. Important differential diagnoses to PCNSLs are gliomas and cerebral infections such as toxoplasmosis and tuberculosis.⁸

Similar to lymphomas related to HIV and PTLD, almost all lymphomas in patients with drug-induced immunosuppression are EBV driven. Therefore, detection of EBV in the CSF can be a diagnostic clue in these patients.

An association between different types of immunomodulatory drugs and development of PCNSL has been described earlier, for example, by Kleinschmidt-DeMasters *et al.*⁷ They described four cases of PCNSL in elderly patients with autoimmune disorders.

The study was primarily focused on the drug mycophenolate mofetil, but two of the patients had a history of treatment with thiopurines. Both the radiological and pathological findings matched our case despite the difference in underlying disorder and medical treatment. The striking difference was the age of our patient. To the best of our knowledge, PCNSL related to the use of thiopurines has never before been described in a younger adult.

Compared with the overall number of patients with IBD treated with thiopurines, only a small fraction develops lymphoma. Bewtra² found that the 'number needed to treat to cause one lymphoma' in patients treated with thiopurines was 4357 for the age 20–29 and 355 for the age >65. PCNSL is even rarer. It is therefore important that the risk of lymphoma should be balanced against the risk of discontinuing treatment, which could lead to relapse in as many as every fourth patient with IBD.² Nevertheless, this case serves to remind that intracranial lymphoma must be considered in any immunocompromised patient presenting with focal neurological findings, and that the finding of EBV in the CSF and characteristic radiological findings can serve as a diagnostic help.

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Learning points

- Treatment with azathioprine may cause severe CD4 lymphocytopenia.
- Immunosuppression increases the risk of developing malignant lymphomas.
- Primary central nervous system (CNS) lymphomas in immunocompromised patients are often Epstein-Barr virus (EBV) driven, and EBV DNA can be found in the cerebrospinal fluid.
- Apart from the finding of EBV DNA in cerebrospinal fluid the diagnosis is supported by characteristic radiological findings.
- Opportunistic infections must always be considered in immunocompromised patients presenting with CNS lesions.

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